



YOYO BITTERS, A POTENT ALTERNATIVE HERBAL DRUG IN THE TREATMENT OF DIABETES

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ABSTRACT

The antidiabetic potentials of yoyo bitters compared with known antidiabetic drug, glibenclamide were studied in Aloxan induced diabetic rats for the period of 28 days. Yoyo bitters at high dose of 23.24 ml/kg-1 effected a significant reduction ($P < 0.01$) in blood glucose level as compared to the controls, without glibenclamide and glibenclamide treatment on days 14, 21 and 28 days. However, there was a significant ($P < 0.001$) fasting blood glucose level on day 7 as compared to glibenclamide treated group. At the median dose of 15.49ml/kg-1 yoyo bitters produced a significant ($P < 0.001$) reduction in glucose level at 7, 14, 21 and 28 days as compared to glibenclamide treated group. Yoyo bitters at the low dose of 7.75ml/kg-1 also produced a significant ($P < 0.001$) reduction in fasting blood glucose levels on days 7, 14, 21 and 28 days compared to glibenclamide group. At the 28th day of low dose treatment, yoyo bitters restored the fasting blood glucose level as compared with control, glibenclamide. The blood glucose levels' with yoyo bitters were dose and periodic dependent. The study observed a high antidiabetic potentials of yoyo bitters as that of glibenclamide and could be used as alternative drug in the treatment of diabetes.

Key words: Yoyo bitters, glibenclamide, diabetes.

INTRODUCTION

Diabetes is a metabolic disorder characterized by chronic hyperglycemia resulting from defects of insulin secretion cum pancreatic dysfunction (WHO, 1999). The disease is fast growing world wide, as at 2006 at least 171 million people globally suffered from diabetes it is estimated that in 2030 about 330 million will be affected by the disease, American Diabetic Association, 2010. In Africa about 14.7 million adult are estimated to suffer from diabetes with a regional prevalence of 3.8% with Nigeria having 3.1% as the highest as the mortality rate is also rising, international diabetes Federation, 2011.

The clinical symptoms of diabetes include polyuria i.e frequent voiding of large volume of urine, polydipsia, increased thirst, polyphagia,

increased hunger and increase weight loss. The disease is associated with many complications; ketosis, acidosis, ketoacidosis, cardiovascular diseases, diabetic neuropathy, diabetic retinopathy and diabetic foot amputations. These complications increase the morbidity rates and makes the disease quite dreading, International working group 2011, at the moment there is no satisfactory therapy for the treatment and management of the disease. The few treatment regimens are characterized with several complications e.g. insulin resistance with attendant effects e.g. anorexia, nervosa, brain atrophy and fatty liver particularly in chronic usage of this hormone. Use of amylin analogues – results in hypoglycemia at high dosages, visual disorders, tremor, cerebral convulsion, diarrhoea, bradycondia, thrombocytopenia, hemolytic anaemia, cholestasis, jaundice and hepatitis, Nigerian, German chemical ILC, 2008. Besides, these drugs are quite expensive for the

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low income people. This has made many to resort to herbal application for the treatment of the ailment (Sudha, et al 2009). The world health organization expert committee in diabetes had also recommended traditional application in the management of diabetes, Osinubi, 2006. This is why the study was focused on a current herbal therapy; yoyo bitters.

Yoyo bitters have gained a very wide usage in Nigeria as blood cleanser, other usages as claimed by the producers include enhancement of effective function of the secretory glands, stimulation of the liver for effective functioning, helps in the elimination of cholesterol, sugar triglycerides, creatinine and uric acid, Abllat, Nig. Ltd, 2011. The interest of this study was on the sugar level as our cross sectional questionnaires on adult population proved that this herbal drug reduced blood sugar level. But there are no documented research on this and hence this virgin study to create health care awareness in the use of yoyo bitters as antidiabetic drug. In this study, yoyo bitters is compared with a widely used antidiabetic drug; glibenclamide. Glibenclamide is indicated for the treatment and management of non insulin dependent type 2 diabetes mellitus. It has also been found to improve outcome in animal stroke model via prevention of brain swelling and neuroprotection, Ortega, 2012.

The drug acts by inhibiting the sulfonylurea receptor I which is the regulatory subunit of ATP – sensitive. Potassium channels in pancreatic cells. Inhibition leads to the depolarization of cell membrane opening voltage dependent calcium channel. This action finally results in increase in intracellular calcium in the beta cells and hence the stimulation and release of insulin, Simard, 2006. Adverse effects of glibenclamide are; hypoglycemia, cholestasis, jaundice, hepatitis, thrombocytopenia, haemolytic anaemia, leucopenia, pancytopenia, visual impairment, nausea, diarrhoea though these symptoms do disappear at withdrawal of the drug, but such will aggregate the diabetic situation and may result in a fatal outcome. There is therefore need for physiologic friendly drugs which the disease will not lead to more complications than the disease treatment itself.

MATERIALS AND METHODS

Inducement of diabetes using Alloxan

Alloxan is also known as 2, 4, 5, 6 pyrimideterone, it is or pyrimidine derivative. It is a strong oxidizing agent. Alloxan is a toxic glucose analogue, it selectively destroys insulin producing beta-cells of the pancreas. The beta cell toxic action of alloxan is initiated by free radicals in the redox reaction state, Lenzen, 2008. Alloxan may also induced diabetes via lipolysis of adipocytes this will lead to increase levels of free fatty acid e.g. glycerol. Such will eventually lead to insulin resistance and insulin resistance is the major cause of type 2 diabetes, Kandulsku, 2009.

Methods of Jimmy 2012 and Batta 2007 were used. The rats were fasted for 14 hours, and a single dose of alloxan, 150mg/kg was administered intraperitoneally as 5% W/V in distilled water. The rats were allowed to rest for 72 hours before determining their blood glucose level effects of alloxan. Blood glucose levels of between 200 – 450mg/dL after 72 hours were classified as diabetic.

Grouping of rats:

A total of thirty six (36) adult male rats were used for the study and were grouped into 6 groups. Group 1 was the control group given 10ml of water, group 2 as the alloxan induced group without treatment. Group 3 was also diabetics, induced group but treated with 1.2mg/kg of glibenclamide. Groups 4, 5, 6 were administered 23.4ml/kg 15.49ml/kg and 7.5ml/kg of yoyo bitters, being high dose, median dose and low dose respectively. The drugs were administered orally using orogastric canula, Jimmy et al 2012.

Fasting Blood Glucose Assay:

Blood glucose levels were determined by the use of glucometer. The glucometer was switched on, the code chip was inserted into the meter's slot at the side of the glucometer and the test strip was inserted. Blood was collected by cutting the tip of the rats tail using scissors and the blood dropped at the glucose sensor region of the test strip. The blood glucose levels

were then measured in mg/dL Roche, diagnostics, 2010.

The blood glucose levels were measured for 7, 14, 21 and 28 days.

LD50 of the Yoyo Bitters, (Lorke's method, and Miller, 1983):

This was necessary to ascertain the safety dose of it. Twenty four (24) albino mice which weighed 17-23g were used for this study. They were fasted 24 hours. The mice were divided into six groups, with four mice in a group. Groups 1, 2, 3 were administered intraperitoneally with 10ml/kg 20ml/kg, and 40ml/kg of yoyo bitters, while groups 3, 5, 6 were given 60ml/kg, 80ml/kg and 100ml/kg of yoyo bitters respectively. The rats were observed within 24 hours for signs of effects of the drug. The results observed from this study were used to arrive at the different doses used in the main study; low dose; 7.75ml/kg, medium dose; 15.49ml/kg and high dose; 23.24ml/kg. The different dose range were then used against the different weights of the rats to obtain the real volumes of the yoyo bitters per the animal. The lethal dose was 77.46ml/kg. There was no need to carryout the LD50 for glibenclamide, a standard drug already in use.

RESULTS

In the study high antidiabetic effects have been observed with the administration of yoyo bitters. Using the different dosages, the different dosages of yoyo bitters at periodic intervals of 7, 14, 21 and 21 days showed different results in blood glucose levels. For instance at 7 days with high dosage, it was 229.80 ± 0.54 , 14 days, 141.30 ± 1.69 , 21 days; 91.67 ± 1.68 and at 28 days; 72.33 ± 0.84 . All showed significant difference in reduction, $P < 0.01$ compared with control. For the medium dose; 15.49 ml/kg of yoyo bitters at 7 days, the blood glucose level was 262.00 ± 3.72 , day 14, 177.30 ± 11 and on day 28; 82.88 ± 0.75 , the reductions were significant $P < 0.001$, as compared with controls. In the low dose, 7.75 ml/kg, day 7 had the following, blood glucose level; 288.30 ± 0.67 day 14; 243.00 ± 0.58 , day 21; 186.80 ± 0.58 , day 28; 137.83 ± 0.95 . The results were significant at $P < 0.001$ as

compared with controls. Comparing the yoyo bitters in the 1.2mg/kg glibenclamide, the following results were obtained, day 7, 205.20 ± 1.83 , day 14, 114.70 ± 0.84 , day 21; 82.33 ± 0.95 , and day 28; 62.50 ± 0.62 . The results were significantly different, $P < 0.001$ when compared with controls.

DISCUSSION

The study has unveiled a high antidiabetic potentials of yoyo bitters compared with glibenclamide a widely used orthodox drug in the treatment of diabetes. The potency of the yoyo bitters is proven through its ability to reduce blood glucose of antidiabetic rats. The reduction of blood glucose level by yoyo bitters was dose dependent and at dosage increase. It was observed that as the period of administration increase the effectiveness of the drug also increased. The study was done for only 28 days with a drastic reduction in the blood glucose level, it means that much reduction could be achieved with increase period of administration. Comparatively, 'yoyo bitters seem to have almost same efficacy in blood glucose reduction as glibenclamide if administered for a longer period. It is even a drug with multiple pharmacological effects which stands to benefit the population of various ailments. However, yoyo bitters showed little toxic effects at the lethal dose of 77.46ml/kg in the animal experiment (mice). This is translated to about 5.422.2ml/70kg on man. This calls for review of the recommended dose of this drug. But this drug may not pose much hypoglycemic effects as in the case of glibenclamide except when taken at high dosages. Importantly is that the yoyo bitters drug is not taken as antidiabetic drug and so some one who may be sensitive to this drug, may experience hypoglycemia whereas the person did not know that the drug has antidiabetic properties. It is very necessary that drug producers should find time to screen the concentration of their drugs and indicate the relative pharmacologic actions before distributing for dispensing. However, the health contributions of yoyo bitters are enormous particularly this period of high upsurgence of diabetes. The pharmacologic activity of yoyo bitters as antidiabetic drug may be based on its

ability to stimulate insulin secretion from the beta cells of the pancreas. The mechanism of insulin secretion involves intracellular potassium influx into the beta cells of the pancreas which leads to the depolarization of the cell membrane such leads to activation of voltage sensitive calcium channels and the resulting influx which triggers release of insulin by exocytosis, Seeley, 2011 Ganong 2001. The yoyo bitters has aloe Vera contents which also goes to prove its antidiabetic, hypoglycemic and antioxidant properties Lanjhiyana, 2011. Yoyo bitters may have also stimulated the secretion of glucokinase. This enzyme catalyzes the conversion of glucose to glucose – 6- phosphate which is then polymerized to glucose or catabolized to ATP. The ATP inhibits ATP, sensitive K^+ channels decreasing K^+ efflux and depolarizes the cell membrane to allow calcium influx into the beta cells and the subsequent concentration of insulin. This will enhance glucose utilization by peripheral tissues and thus the reduction of blood glucose. The polymerization of glucose 6 phosphate into glycogen also help to remove excess blood glucose, Guyton, 2006, Hardman, 2001.

A very good attribute of yoyo bitters is its low hypoglycemic activity. Our study has shown that glibenclamide reduced the fasting blood glucose of the diabetic rat below the normal range of fasting blood glucose (70 – 110mg/dL to 62.50 ± 0.62 when compared to that of yoyo bitters which only reduce it to normal range with periodic comparison. The implication is that glibenclamide is associated with hypoglycemic. Our report is in line with previous studies, Kazi, 2008, Hardman 2001. But yoyo bitters drug seems not to be associated with hypoglycemia given at normal dosage. However, hypokalaemia is associated with chronic usage of yoyo bitters, Ekor 2010. Hypokalaemia is associated with cardiac, renal and neurologic dysfunction, Reungjis 2008, Anders 2006, Habils, 2005. There is therefore need of being highly cautious of the dosages and duration of intake of yoyo bitters despite its high antidiabetic potentials.

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